

## Repetitive ventricular response

### *Prevalence and prognostic significance*

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**SUMMARY** The purpose of this study was to determine the prevalence of repetitive ventricular responses caused by non-bundle-branch re-entry and bundle-branch re-entry in 47 patients with and in 50 patients without ventricular tachycardia. We also compared the prevalence of repetitive ventricular responses using two types of electrophysiological stimulation: single premature ventricular stimulation during sinus rhythm or atrial pacing, and single premature ventricular stimulation during ventricular pacing. In patients who had ventricular tachycardia, premature ventricular stimulation during ventricular pacing induced non-bundle-branch re-entry more often than during atrial pacing (70.2% versus 33.3%). Both methods of stimulation induced non-bundle-branch re-entry more often in patients who had ventricular tachycardia than in those who did not. In both groups of patients, bundle-branch re-entry was rare during atrial pacing and more common but equally prevalent during ventricular pacing.

To determine if induced non-bundle-branch re-entry could identify patients at risk of developing future symptomatic ventricular tachycardia or sudden death, 59 patients who had a history of documented ventricular tachycardia had an electrophysiological study just before discharge and were followed for an average of 10.9 months. Non-bundle-branch re-entry induced during ventricular and atrial pacing had a predictive accuracy of 59% and 64%, respectively. The predictive accuracy of non-bundle-branch re-entry induced during atrial pacing appeared to be greater in patients who also had ventricular tachycardia induced during the same electrophysiology study. Our data indicate that: (1) non-bundle-branch re-entry is induced more often during ventricular pacing than during atrial pacing and more often in patients who have a history of ventricular tachycardia than in those who do not; (2) induction of non-bundle-branch re-entry during ventricular pacing is more sensitive and during atrial pacing is more specific; however, neither alone yields a predictive accuracy sufficiently high to make the test clinically useful; and (3) induced non-bundle-branch re-entry during atrial pacing associated with induced ventricular tachycardia may define a high risk group.

Sudden death is a critical contemporary medical problem which in most cases is thought to result from ventricular fibrillation. Though previous reports<sup>1-3</sup> noted that the presence of ventricular arrhythmias increased the risk of sudden death, it would be useful to have a test that reliably identified patients at risk of developing symptomatic ventricular tachycardia and sudden death. Greene *et al.*<sup>4</sup> suggested that the repetitive ventricular response, defined as "two or more ventricular complexes in response to a single

ventricular premature stimulus during control of the heart rate by atrial pacing", may serve as such a predictive test. Data from other laboratories<sup>5-9</sup> have not confirmed Greene's results, though in some of these studies<sup>5-7</sup> repetitive ventricular responses were induced during ventricular pacing. In addition, previous reports<sup>4,6,9</sup> concerning prognosis have not distinguished between repetitive ventricular responses caused by bundle-branch re-entry, which appears to be physiological,<sup>10-12</sup> and non-bundle-branch re-entry, which appears to have a higher association with organic heart disease.<sup>12</sup>

We undertook this study for the following purposes: (1) to determine the prevalence of repetitive ventricular

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responses caused by non-bundle-branch re-entry and bundle-branch re-entry in patients who had and did not have a history of ventricular tachycardia; (2) to compare the prevalence of both forms of repetitive ventricular responses using two types of electrophysiological stimulation namely, single premature ventricular stimulation during sinus rhythm or atrial pacing, and single premature ventricular stimulation during ventricular pacing; and (3) to determine if the induction of non-bundle-branch re-entry could be used to identify those patients at risk of subsequently developing symptomatic ventricular tachycardia or sudden death.

### Subjects and methods

Retrospective analysis of 148 electrophysiology studies performed in 125 patients between May 1978 and January 1980 forms the basis of this report. Fifty-one studies were carried out in patients who were receiving antiarrhythmic drugs and 97 control studies in patients who were not. All patients underwent electrophysiological study in the non-sedated, postabsorptive state after giving written informed consent. One to four multipolar electrode catheters were introduced percutaneously via the antecubital and/or femoral veins, and positioned under fluoroscopic guidance in the high right atrium, across the tricuspid valve to record the His bundle electrogram, and in the right ventricular apex and/or right ventricular outflow tract. Pacing was performed with a programmable stimulator (Medtronic No. 5325) which delivered square-wave impulses at twice the diastolic threshold with a pulse duration of 1.8 ms. Intracardiac electrogram recordings, filtered at 30 to 500 Hz, and standard electrocardiographic leads I, II, III, and V<sub>1</sub>, filtered at 0.1 to 20 Hz, were displayed on a multichannel oscilloscope (Electronics for Medicine VR-12) and recorded at paper speeds of 50–150 mm/s.

To induce repetitive ventricular responses, single premature ventricular stimuli were introduced after every eighth beat beginning in late diastole during sinus rhythm or control of the heart rate by atrial pacing and/or ventricular pacing. The premature interval was decreased by 10 to 20 ms steps until a repetitive ventricular response was induced or ventricular refractoriness was reached. In 93% of the studies more than one pacing cycle length and in 81% of the studies more than one right ventricular pacing site (apex and outflow tract) were used during ventricular pacing. During atrial pacing, a second ventricular pacing site was used in 22% and a second atrial pacing cycle length was used in 16% of the patients who did not have a repetitive ventricular response induced at the first ventricular site or pacing cycle length tested. The pacing procedure used to induce ventricular tachycardia has been described previously in detail.<sup>13</sup>

### DEFINITIONS

A *repetitive ventricular response* was defined as two or more premature ventricular complexes produced by a single premature ventricular stimulus delivered during sinus rhythm, atrial pacing, or ventricular pacing. Repetitive ventricular responses were subclassified into probable and possible bundle-branch re-entry and probable non-bundle-branch re-entry. A repetitive ventricular response was interpreted as *probable bundle-branch re-entry* only if it occurred after a critical V<sub>2</sub>H<sub>2</sub> delay and had an H<sub>2</sub>V<sub>3</sub> interval greater than or equal to the HV interval of the conducted supraventricular complexes (Fig. 1).<sup>11,12</sup> V<sub>2</sub>H<sub>2</sub> intervals long enough to result in a repetitive ventricular response occurred only at premature intervals near the ventricular effective refractory period. The QRS morphology of the repetitive ventricular response was usually similar to the QRS complex induced by right ventricular apical pacing. When a His bundle electrogram could not be recorded or no His bundle electrode catheter was used (15.5% of studies), a repetitive ventricular response was classified as *possible bundle-branch re-entry* if it was present only after S<sub>1</sub>S<sub>2</sub> intervals near the ventricular effective refractory period, and the contour was similar to the QRS complex induced by right apical pacing. For the total prevalence of bundle-branch re-entry all probable and possible bundle-branch re-entry responses were added together. All other repetitive ventricular responses were inter-

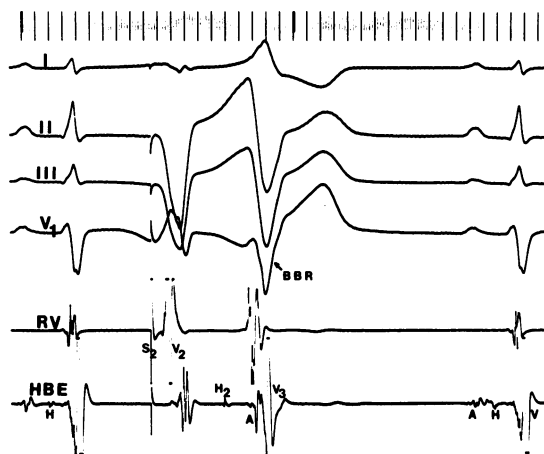


Fig. 1 Demonstration of bundle-branch re-entry (BBR) induced during sinus rhythm after a premature ventricular stimulus (S<sub>2</sub>). Note that the H<sub>2</sub>V<sub>3</sub> interval (80 ms) exceeds the HV interval (60 ms) during sinus rhythm. I, II, III, V<sub>1</sub>—scalar electrocardiographic leads; H<sub>2</sub>—retrograde His potential from V<sub>2</sub>; HBE—His bundle electrogram lead; RV—right ventricular electrogram; S<sub>2</sub>—premature ventricular stimulus; V<sub>2</sub>—ventricular response induced by S<sub>2</sub>; V<sub>3</sub>—spontaneous BBR beat.

preted as non-bundle-branch re-entry. Non-bundle-branch re-entry usually had a configuration different from the complex induced by right ventricular apical pacing and the  $H_2V_3$  interval was either shorter than the HV interval of conducted supraventricular complexes, or more often, no His potential was discernible (Fig. 2). *Induced ventricular tachycardia* was defined as three or more consecutive ventricular complexes induced by programmed stimulation.

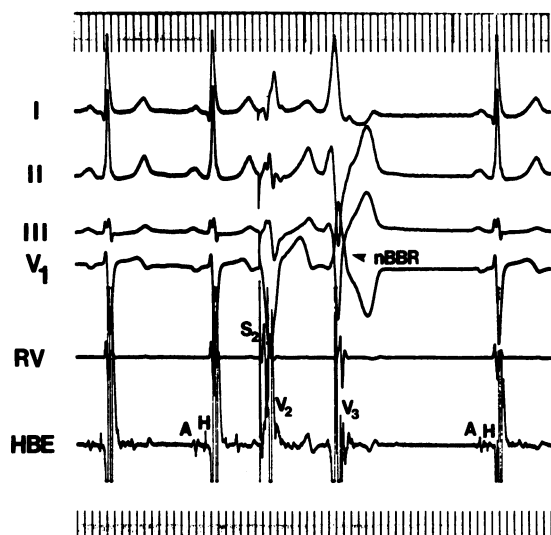


Fig. 2 Demonstration of non-bundle-branch re-entry (nBBR) induced during sinus rhythm after a premature ventricular stimulus ( $S_2$ ). Note that the nBBR beat has a different configuration from the paced ventricular complex ( $V_2$ ) and that no His potential is recorded before the nBBR beat. Abbreviations: as in Fig. 1.

*Symptomatic ventricular tachycardia* was defined as an electrocardiographically documented episode of ventricular tachycardia causing symptoms related to haemodynamic compromise; this included cardiac arrest from which a patient was successfully resuscitated. *Sudden death* was defined as death that occurred within one hour of the onset of symptoms in a patient who had been asymptomatic in the preceding 24 hours, and in whom no other cause of death was identified by history or necropsy. *Positive follow-up* was defined as the occurrence of either symptomatic ventricular tachycardia or sudden death in patients who had a discharge electrophysiology study.

#### PROGNOSIS

Only discharge studies were used to determine the prognostic significance of induced repetitive ventricular responses. Discharge studies were defined as: (1)

studies in the control state after which the patients were discharged receiving no antiarrhythmic drugs, or (2) studies performed in patients who received the same antiarrhythmic medication at study and during the follow-up period. Follow-up information was obtained from personal examination of the patients, from the referring physicians, or from telephone interview of the patients.

#### STATISTICAL METHODS

$\chi^2$  analysis and/or z-tests of significance of the difference between uncorrelated proportions were used to calculate statistical significance. In the statistical analysis of the prognostic data, the following definitions were used:

*True positive*: non-bundle-branch re-entry present on discharge study with occurrence of positive follow-up.

*True negative*: non-bundle-branch re-entry not present on discharge study with no occurrence of positive follow-up.

*False positive*: non-bundle-branch re-entry present on discharge study with no occurrence of positive follow-up.

*False negative*: non-bundle-branch re-entry not present on discharge study with the occurrence of positive follow-up.

In the following equations, non-bundle-branch re-entry is abbreviated as nBBR.

$$\text{Sensitivity} = \frac{\text{True}+}{\text{True}+ \text{ and False}-}$$

or

$$\frac{\text{all nBBR} + \text{positive follow-up}}{\text{all patients} \rightarrow \text{positive follow-up}}$$

$$\text{Specificity} = \frac{\text{True}-}{\text{True}- \text{ and False}+}$$

or

$$\frac{\text{all nBBR} - \text{no positive follow-up}}{\text{all patients} \rightarrow \text{no positive follow-up}}$$

$$\text{Predictive accuracy} = \frac{\text{True}+ \text{ and True}-}{\text{Total number of patients}}$$

#### Results

##### (A) PATIENTS

Ninety-seven patients (68 men, 29 women; mean age 44.0 years) underwent an electrophysiological study when not receiving drugs. Forty-seven patients (mean age 47.9 years) had a prior history of ventricular tachycardia. Of these 23 had coronary artery disease (17 had had a myocardial infarction more than three months

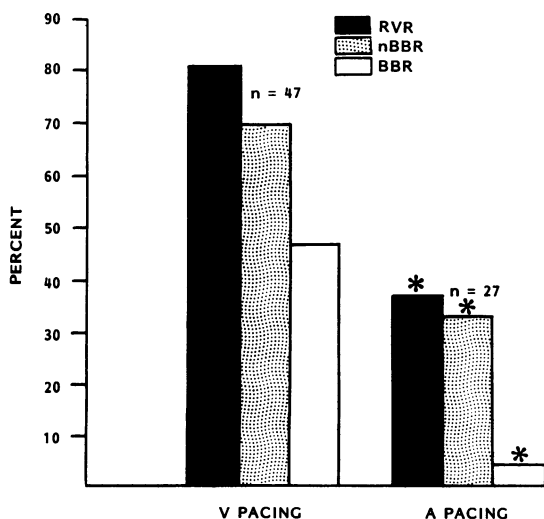
**Table 1** Prevalence of repetitive responses (RVR) caused by non-bundle-branch re-entry (nBBR) and bundle-branch re-entry (BBR) induced at time of control study by single premature ventricular stimulus introduced during ventricular and atrial pacing in patients with and without a history of ventricular tachycardia (VT)

	VT (N=47)		Non-VT (N=50)	
	Ventricular pacing	Atrial pacing	Ventricular pacing	Atrial pacing
No	47	27	50	21
RVR	38 (80.9%)	10 (37.0%)	33 (66.0%)	2 (9.5%)
nBBR	33 (70.2%)	9 (33.3%)	15 (30.0%)	1 (4.8%)
BBR	22 (46.8%)	1 (3.7%)	28 (56.0%)	2 (9.5%)

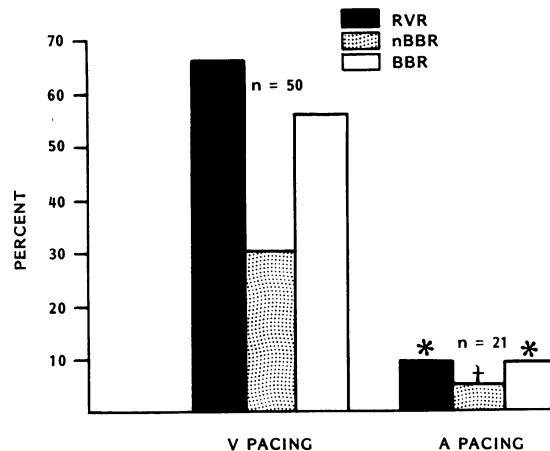
previously and six had angina without a history of prior myocardial infarction), nine had cardiomyopathy, seven had mitral valve prolapse, six had primary electrical disease, and two had valvular heart disease. Fifty patients (mean age 40.5 years) had no prior history of ventricular tachycardia. In this group, 18 had a history of supraventricular tachycardia and no evidence of pre-excitation, 15 had pre-excitation syndromes, nine had syncope of undetermined aetiology, and eight had conduction abnormalities.

#### (B) PREVALENCE OF REPETITIVE VENTRICULAR RESPONSES

A single premature ventricular extrastimulus was introduced during ventricular pacing in all 97 patients, and during either sinus rhythm or atrial pacing in 48



**Fig. 3** Prevalence of repetitive ventricular responses (RVR) induced during ventricular (V) and atrial (A) pacing at control study in 47 patients who had a history of ventricular tachycardia (VT). BBR—bundle-branch re-entry; nBBR—non-bundle-branch re-entry; \* $p < 0.001$ .



**Fig. 4** Prevalence of repetitive ventricular responses (RVR) induced during ventricular (V) and atrial (A) pacing at control study in 50 patients with no history of ventricular tachycardia. Abbreviations: As in Fig. 3; \* $p < 0.05$ .

patients. For simplicity, testing during sinus rhythm or atrial pacing was considered as one group designated as atrial pacing. The prevalence of repetitive ventricular responses using both stimulation techniques is shown in Table 1. In the 47 patients who had ventricular tachycardia (Fig. 3), and in the 50 patients who did not have ventricular tachycardia (Fig. 4), both non-bundle-branch re-entry and bundle-branch re-entry occurred more often during ventricular pacing than during atrial pacing. As shown in Table 1, non-bundle-branch re-entry was induced more often ( $p < 0.001$ ) by both pacing methods in patients who had ventricular tachycardia compared with those patients who did not. In addition to the 97 studies performed in the control state, 51 studies were performed in patients taking antiarrhythmic drugs. The prevalence of repetitive ventricular responses was not statistically different between these and those who were not taking drugs.

#### (C) PROGNOSTIC SIGNIFICANCE OF

##### NON-BUNDLE-BRANCH RE-ENTRY IN PATIENTS WITH A HISTORY OF VENTRICULAR TACHYCARDIA

Fifty-nine patients who had a history of ventricular tachycardia underwent discharge electrophysiological study. During a mean follow-up period of 10.9 months, 17 patients had symptomatic ventricular tachycardia, and nine patients died (seven sudden deaths; two non-sudden deaths). Table 2 shows the sensitivity, specificity, and predictive accuracy of non-bundle-branch re-entry induced at discharge study. Non-bundle-branch re-entry induced during ventricular pacing was more sensitive ( $p < 0.05$ ), and during atrial pacing was more specific ( $p < 0.05$ ); both pacing techniques, however, had a low predictive accuracy.

Table 2 Prognostic indices of non-bundle-branch re-entry (nBBR) in patients who had history of ventricular tachycardia

Atrial pacing		Ventricular pacing	
No.		No.	
33	{ 11 nBBR+→6 VT-S, 2SD 22 nBBR→7 VT-S, 2SD	59	{ 35 nBBR+→11 VT-S, 6SD 24 nBBR→5 VT-S, 1SD
Sensitivity	47%†		74%
Specificity	81%†		50%
Predictive accuracy	64%		59%

Abbreviations: VT-S, symptomatic ventricular tachycardia; SD, sudden death; † $p < 0.05$  compared with ventricular pacing.

(D) PROGNOSTIC SIGNIFICANCE OF INDUCED VENTRICULAR TACHYCARDIA ASSOCIATED WITH INDUCED NON-BUNDLE-BRANCH RE-ENTRY DURING ATRIAL PACING IN PATIENTS WHO HAD A HISTORY OF VENTRICULAR TACHYCARDIA Sixteen patients with ventricular tachycardia induced by programmed electrical stimulation at the time of their discharge electrophysiological study also had atrial pacing performed in an attempt to induce repetitive ventricular responses. As shown in Fig. 5, eight patients had non-bundle-branch re-entry induced during atrial pacing, and in seven recurrent symptomatic ventricular tachycardia or sudden death occurred. In contrast, of eight patients who did not have non-bundle-branch re-entry induced, only two patients had symptomatic ventricular tachycardia, and there were no sudden deaths ( $<0.05$ ).

#### (E) PROGNOSTIC SIGNIFICANCE OF BUNDLE-BRANCH RE-ENTRY

During ventricular pacing, bundle-branch re-entry was present in 46.8% of patients who had a history of ventricular tachycardia and in 56.0% of patients who did not have a history of ventricular tachycardia. At discharge study, induction of only bundle-branch re-entry (no non-bundle-branch re-entry complexes) occurred in 22 patients during ventricular pacing and in five patients during atrial pacing. One patient in each group had spontaneous symptomatic ventricular tachycardia during follow-up, and both of these patients had a previous history of ventricular tachycardia.

#### (F) ABILITY OF NON-BUNDLE-BRANCH RE-ENTRY TO PREDICT FUTURE EVENTS IN PATIENTS WHO DID NOT HAVE A HISTORY OF VENTRICULAR TACHYCARDIA

No patient in the group who did not have a history of ventricular tachycardia had ventricular tachycardia induced by programmed electrical stimulation. Fifteen patients had non-bundle-branch re-entry induced

during ventricular pacing at their discharge study, but no patient had symptomatic ventricular tachycardia during the follow-up period. One patient without a previous history of ventricular tachycardia died suddenly during follow-up. Non-bundle-branch re-entry was not induced in this patient using either pacing technique.

## Discussion

### PREVALENCE OF REPETITIVE VENTRICULAR RESPONSES DURING ATRIAL PACING—COMPARISON WITH OTHER STUDIES

Induction of repetitive ventricular responses during atrial pacing in only 37% of patients who had a history of ventricular tachycardia differs considerably from the 88% previously reported by Greene *et al.*<sup>4</sup> This discrepancy may be explained in part by one or more of the following. First, they routinely tested a second right ventricular site if no repetitive ventricular response was found at the first site. The fact, however, that they increased their yield of induced repetitive ventricular responses by only 14%<sup>14</sup> makes this reason alone unlikely. A second consideration may be whether or not their patients were on antiarrhythmic drugs at the time of study, since these were continued in some cases by them. In our study, we found no significant difference in the frequency of repetitive ventricular response induction between studies performed in patients on or off antiarrhythmic drugs, which suggests, therefore, that these were not a factor. A third possibility is that many of their studies were performed without recording a His bundle electrogram so that some aberrantly conducted supraventricular beats may have been misclassified as repetitive ventricular responses. A fourth factor may be the difference between the duration of the stimulus used in our study (1.8 ms) compared with that used by these workers<sup>4</sup> (0.9 ms). Our data are more consistent with those reported by Mason<sup>8</sup> and Ruskin and Garan.<sup>9</sup>

### PREVALENCE OF REPETITIVE VENTRICULAR RESPONSES DURING VENTRICULAR PACING—COMPARISON WITH OTHER STUDIES

Both categories of repetitive ventricular responses were more prevalent during ventricular pacing than during atrial pacing. The overall prevalence of repetitive ventricular responses during ventricular pacing in our study closely correlates with that previously described by Farshidi *et al.*<sup>12</sup> Non-bundle-branch re-entry, however, was more frequently observed (51.5%) in the total population than previously reported (19.5%).<sup>12</sup> The difference in the frequency of non-bundle-branch re-entry may relate to a difference in patient population or may be the result of our method of testing multiple sites and pacing cycle lengths.

## BUNDLE-BRANCH RE-ENTRY: PREVALENCE AND SIGNIFICANCE

Greene *et al.*<sup>14</sup> suggested that bundle-branch re-entry was rarely induced during atrial pacing and that virtually all repetitive ventricular responses induced by this method were the result of non-bundle-branch re-entry. During atrial pacing we noted bundle-branch re-entry in three of 48 studies (6.3%). Therefore, bundle-branch re-entry can occur using this technique (Fig. 1) and our prevalence compares closely with the previously reported value of 6.7%.<sup>8</sup> Furthermore, bundle-branch re-entry comprised 25% (3/12) of all the repetitive ventricular responses observed during atrial pacing. It cannot therefore be assumed that all repetitive ventricular responses induced during atrial pacing are secondary to non-bundle-branch re-entry particularly when a His bundle electrogram is not available.

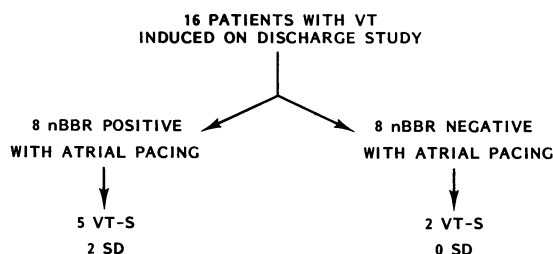


Fig. 5 Follow-up data of 16 patients who had ventricular tachycardia (VT) induced on their discharge study, and who also had atrial pacing performed. Of the eight patients who had non-bundle-branch re-entry (nBBR) during atrial pacing, five developed symptomatic ventricular tachycardia (VT-S), and two died suddenly (SD). Of the eight patients who did not have nBBR, only two had VT-S and none died suddenly (SD).

Only one of 22 patients who had only bundle-branch re-entry initiated during ventricular pacing had symptomatic ventricular tachycardia during follow-up. In addition, the frequency of bundle-branch re-entry was similar whether or not patients had a previous history of ventricular tachycardia. The low association of bundle-branch re-entry with a morbid event supports previous work<sup>10-12</sup> suggesting that bundle-branch re-entry induced during ventricular pacing is common and probably physiological.

In our study, only one of five patients who had bundle-branch re-entry alone only during atrial pacing developed spontaneous symptomatic ventricular tachycardia. Mason<sup>8</sup> previously reported no sudden deaths in four patients who had bundle-branch re-entry during atrial pacing. Therefore, bundle-branch re-entry induced during atrial pacing may also be physiological; the small number of patients reported to

date, however, makes the prognostic importance of this phenomenon as yet uncertain.

**PROGNOSTIC IMPLICATIONS OF NON-BUNDLE-BRANCH RE-ENTRY IN PATIENTS WITH HISTORY OF VENTRICULAR TACHYCARDIA**  
In our study, the predictive accuracy of non-bundle-branch re-entry during atrial pacing was 64% (Table 2). Nine patients who did not have non-bundle-branch re-entry induced during atrial pacing developed, however, a spontaneous morbid event. Therefore, though this test was reasonably specific (81%), it was not very sensitive (47%) because of the higher number (nine) of false negative results.

Non-bundle-branch re-entry was induced more frequently during ventricular pacing than atrial pacing. Though more sensitive, however, ventricular pacing lost specificity because of the higher number of false positive responses. Therefore, the resultant predictive accuracy (59%) with ventricular pacing was not statistically different from that with atrial pacing.

#### INCREASED RISK IN PATIENTS WITH VENTRICULAR TACHYCARDIA INDUCED IN ADDITION TO NON-BUNDLE-BRANCH RE-ENTRY DURING ATRIAL PACING

Though induced non-bundle-branch re-entry during atrial pacing did not adequately predict future symptomatic events, if ventricular tachycardia was also induced the combination appeared to be a risk factor. As shown in Fig. 5, patients who had this combination induced during electrophysiological study had a greater prevalence of future morbid events than those patients who had ventricular tachycardia induced without non-bundle-branch re-entry. A single premature ventricular stimulus delivered during sinus rhythm or atrial pacing may simulate more closely the spontaneous initiating event leading to ventricular tachycardia or fibrillation. Further prospective studies with a larger patient population are needed to verify this finding.

#### PROGNOSTIC SIGNIFICANCE OF NON-BUNDLE-BRANCH RE-ENTRY IN PATIENTS WITHOUT PREVIOUS HISTORY OF VENTRICULAR TACHYCARDIA

Our results confirm previous work<sup>15</sup> showing that ventricular tachycardia is rarely initiated by programmed electrical stimulation in patients without a history of spontaneous ventricular tachycardia. In 62 electrophysiological studies in patients with no previous history of ventricular tachycardia, ventricular tachycardia could not be initiated, whether or not the patients received an antiarrhythmic drug at the time of study. In those patients without ventricular tachycardia, non-bundle-branch re-entry was induced in

30% during ventricular pacing and in 4-8% during atrial pacing. Since none of these patients had symptomatic ventricular tachycardia or sudden death, treatment to suppress non-bundle-branch re-entry in this group does not appear to be warranted.

## Conclusions

Our data indicate that: (1) non-bundle-branch re-entry is induced more frequently during ventricular pacing than during atrial pacing and more often in patients with ventricular tachycardia than in those without; (2) in patients with ventricular tachycardia, induction of non-bundle-branch re-entry during ventricular pacing is more sensitive and during atrial pacing is more specific; neither alone, however, has sufficiently great predictive accuracy to make the test clinically useful; and (3) induction of both non-bundle-branch re-entry during atrial pacing and ventricular tachycardia by any stimulation method may define a high risk group.

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